Metabolically-driven epigenetic changes in iPSC reprogramming

Grant Award Details

Metabolically-driven epigenetic changes in iPSC reprogramming

Grant Type: Basic Biology V

Grant Number: RB5-07384

Project Objective: To understand the role of the Estrogen Related Receptor alpha (ERRα) in mediating metabolic and epigenetic changes during early reprogramming of human cells.

Investigator:

Name:	Ronald Evans
Institution:	Salk Institute for Biological Studies
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,491,900

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title:	Metabolically-driven epigenetic changes in iPSC reprogramming
Public Abstract:	Generation of induced pluripotent stem cells (iPSCs) from somatic cells through cellular reprogramming offers tremendous potential for therapeutics, the study of disease states, and elucidation of developmental processes. Central to the process of generating a pluripotent cell from a somatic cell is an energy-dependent epigenetic reconfiguration event that must occur to produce iPSCs with characteristics similar to embryonic stem cells. However, the identity of nuclear factors that activate the metabolic programs linked to pluripotency and their contribution to epigenetic reprogramming remains largely unclear. Our lab is known for its discovery of the family of nuclear hormone receptors (NHRs) that use hormones to control genes and thereby regulate embryonic development, physiology and metabolism. Utilizing our specialized NHR knowledge and tools we identified a sub-population of cells that arise early in reprogramming that transiently express the NHR Estrogen Related Receptor alpha (ERRα). These rare cells provide the principal reservoir from which iPSC cells are produced. Utilizing this newly identified cell population, we will determine the metabolic pathways during cellular reprogramming that reestablish ES cell-like chromatin patterns. Understanding the mechanism of epigenetic resetting could be exploited to deal with adult diseases such as cancer or even in 'rejuvenating' aged cells.
Statement of Benefit to California:	Our focus is on nuclear hormone receptors (NRs) that use hormones to control genes that regulate development, growth, and physiology. This has brought in more than $100M in private and federal funding to this lab over the last 30 years and has led to employment of 150+ people, publication of over 350 papers, and founding of three biotech companies that in aggregate raised more than $1B in research and development support. Several FDA-approved drugs for cancer, diabetes, osteoporosis, and leukopenia were developed with this technology. We found that a unique subset of 38 NRs are expressed in adipose-derived human induced pluripotent stem cells (hiPSCs), but little is known of how they control stem cell renewal and differentiation. Potential use of the extensive family of hormonal ligands to control iPSC generation, maintenance, and cell fate has profound implications for regenerative medicine. We wish to use our expertise to understand how NRs can be exploited to accelerate the use of iPSCs in regenerative medicine. Our proposed study should be beneficial to the State of California and its citizens in several ways: 1) by maintaining a unique training environment for students, postdocs and physicians; 2) discovering how to more efficiently generate and use human iPSCs; 3) deciphering the molecular genetic logic of nuclear reprogramming; 4) determining how a pharmacopeia of hormones and drugs can be brought to bear on directing stem cell renewal, differentiation, and therapy.